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Rapid and Efficient Pd-Catalyzed Sonogashira Coupling of Aryl Chlorides

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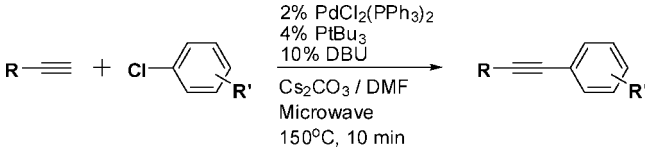
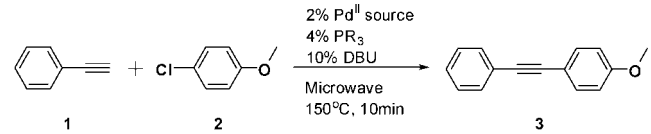


An efficient and effective microwave-assisted cross-coupling of terminal alkynes with various aryl chlorides including sterically hindered, electron-rich, electron-neutral, and electron-deficient aryl chloride is developed. It proceeds faster and generally gives good to excellent yields and also can be extended successfully to the Suzuki coupling and Buchwald−Hartwig amination, as well as the Heck coupling with inert aryl chlorides. The short reaction times and simple reaction conditions coupling with a broad substrate scope render this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules.

Transition-metal-mediated cross-coupling reactions represent extremely powerful and versatile methods in organic synthesis.[1] Reactions leading to C(sp)−C(sp^2) bond formation are often key steps in a wide range of organic processes.[2] Among these, the Sonogashira reaction, involving the coupling of aryl or vinyl halides with terminal alkynes, has emerged as a favorite.[3] One current challenge associated with Sonogashira coupling reaction is its inefficiency when "unreactive" aryl chlorides are employed as coupling partners in virtue of increased availability and decreased expense of aryl chlorides relative to aryl bromides and iodides. To date, only limited success has been obtained in the Sonogashira cross-coupling of alkynes with aryl chlorides. The state of the art in the area includes utilizing the $P(Cy)_2Ar$ as ligand, reported by Buchwald and co-workers.[4a] Eberhard and Plenio et al. have achieved significant success with zinc or palladium catalysts.[4b–e] Recently, Hua and Li et al. have reported efficient catalyst systems using $PdCl_2(PCy_3)_2$ as catalyst or TBAF as promoter.[4f,g] Although these methods are highly effective, there is still much room for improvement. For example, the requirement of long reaction times is a shortcoming in the method of Eberhard, and low substrate generality is also a problem in the methods of Hua and Li. Therefore, the purpose of our research work is to develop an effective, copper-free, easily available catalyst condition for Sonogashira coupling of a wide variety of aryl chlorides. Developing catalytic systems that perform more efficiently with aryl chlorides in short times is an ongoing effort. Herein we described cross-couplings of terminal alkynes with various aryl chlorides including sterically hindered, electron-rich, electron-neutral, and electron-deficient aryl chloride in excellent yield with commercially available reagents under microwave (MW) irradiation.

TABLE 1. Optimization of Catalysis Conditions[a]



entry	solvent	palladium	phosphane	base	yield [%]
1	DMSO	$PdCl_2(PPh_3)_2$			0
2	DMSO	$PdCl_2(PPh_3)_2$	PPh_3		<5
3	DMSO	$PdCl_2(PPh_3)_2$	$PtBu_3$		53
4	DMSO	$PdCl_2$	$PtBu_3$		<5
5	DMSO	$Pd(OAc)_2$	$PtBu_3$		<5
6	DMSO	$PdCl_2(PPh_3)_2$	$PtBu_3$	Cs_2CO_3	78
7	DMSO	$PdCl_2(PPh_3)_2$	$PtBu_3$	NaOMe	70
8	DMSO	$PdCl_2(PPh_3)_2$	$PtBu_3$	NaOEt	68
9	DMF	$PdCl_2(PPh_3)_2$	$PtBu_3$	Cs_2CO_3	84

[a] Reaction conditions: 2% Pd source, 4% phosphane (except entry 1), 10% DBU, 1.0 equiv base, 150 °C, 10 min.

Consistent with other cross-coupling processes, the Sonogashira reaction proceeds more rapidly with more electron-poor halides.[4] In this study, we chose the cross-coupling of phenylacetylene (**1**) and *p*-chloroanisole (**2**), a relatively challenging test substrate because of its electron-richness, as the model reaction to screen the catalysts and optimize the reaction

(1) For recent reviews on this topic, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

(2) For selected references, see: (a) Cwik, A.; Hell, Z.; Figueras, F. *Tetrahedron Lett.* **2006**, *47*, 3023. (b) Ruiz, J.; Cutillas, N.; López, F.; López, G.; Bautista, D. *Organometallics* **2006**, *25*, 5768. (c) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729. (d) Li, J.-H.; Li, J-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053. (e) Choudary, B. M.; Madhi, S.; Kantam, M. L.; Sreedhar, B.; Iwasawa, Y. *J. Am. Chem. Soc.* **2004**, *126*, 2292. (f) González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1536. (g) Li, J.-H.; Zhang, X.-D.; Xie, Y.-X. *Eur. J. Org. Chem.* **2005**, 4256. (h) Méry, D,; Heuzé, K.; Astruc, D. *Chem. Commun.* **2003**, *15*, 1934.

(3) (a) For recent reviews on Sonogashira reaction, see: Doucet, H.; Hierso, J. -C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (b) Chinchilla, R.; Carmen Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

(4) For representative papers on the Sonogashira cross-coupling reactions of aryl chlorides with alkynes, see: (a) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993. (b) Eberhard, M. R.; Wang, Z. H.; Jensen, C. M. *Chem. Commun.* **2002**, *8*, 818. (c) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056. (d) Remmele, H.; Köllhofer, A.; Plenio, H. *Organomet.* **2003**, *22*, 4098. (e) Fleckenstein, C. A.; Plenio, H. *Organomet.* **2007**, *26*, 2758. (f) Yi, C. Y.; Hua, R. M. *J. Org. Chem.* **2006**, *71*, 2535. (g) Liang, Y.; Xie, Y. -X.; Li, J. -H. *J. Org. Chem.* **2006**, *71*, 379. (h) Protti, S.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5675. (i) Heuzé, K.; Méry, D.; Gauss, D.; Blais, J. -C.; Astruc, D. *Chem. Eur. J.* **2004**, *10*, 3936. (j) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127. (k) Yi, W.-B.; Cai, C.; Wang, X. *Eur. J. Org. Chem.* **2007**, 3445.

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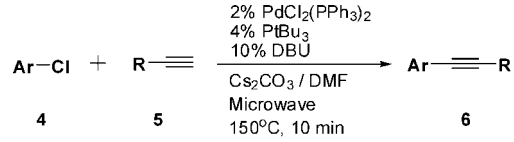
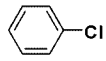
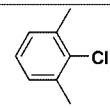
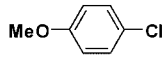
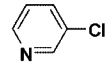
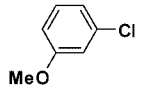
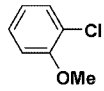
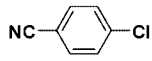
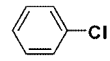
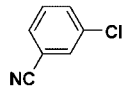
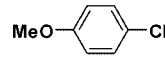
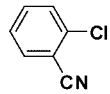
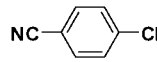
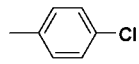
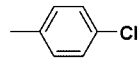
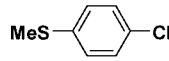
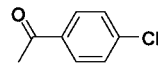
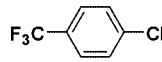
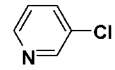
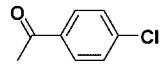
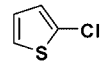
TABLE 2. Sonogashira Coupling of Aryl Chlorides ArCl with Alkynes RC≡CH[a]



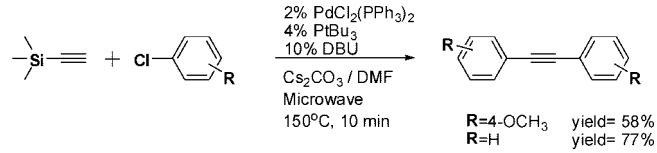
4 5 6

Entry	ArCl	R	Yield [%]	Entry	ArCl	R	Yield [%]
1		Ph	90	12		Ph	79
2		Ph	84	13		Ph	82
3		Ph	83	14		Ph	87
4		Ph	79	15		Ph	81
5		Ph	92	16		n-C_6H_{13}	92
6		Ph	94	17		*n*-C_6H_{13}	88
7		Ph	90	18		n-C_6H_{13}	95
8		Ph	89	19		n-C_6H_{13}	89
9		Ph	76	20		n-C_6H_{13}	94
10		Ph	95	21		n-C_6H_{13}	83
11		Ph	93	22		n-C_6H_{13}	86

[a] Reaction conditions: 2% $PdCl_2(PPh_3)_2$, 4% P*t*Bu_3, 10% DBU, 1.0 equiv of Cs_2CO_3, DMF, 150 °C, 10 min.

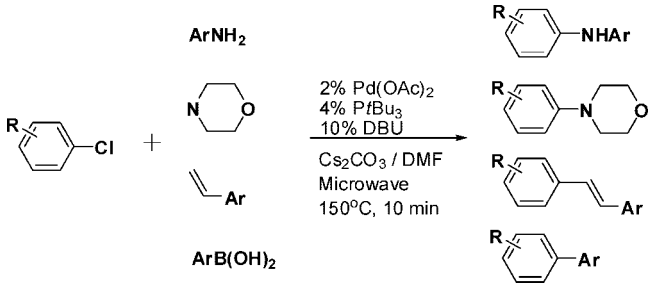
conditions. As illustrated in Table 1, we observed little or no coupling in the absence of phosphane (entry 1) or in the presence of triarylphosphanes and basefree condition (entry 2), indicating that phosphane and base were very crucial to the cross-coupling reaction. The steric bulk and the electron-richness of P*t*Bu_3 are critical for this unprecedented reactivity (entry 3). It was found that the nature of palladium source had a pronounced impact on the process. $PdCl_2(PPh_3)_2$ turned out to be better than $PdCl_2$ and $Pd(OAc)_2$ (entries 3−5, Table 1). The most effective base among those that we have surveyed is Cs_2CO_3 (entry 6). Strong bases (e.g., NaOMe and NaOEt) also accelerated the cross-coupling process but not as effectively as Cs_2CO_3 (entries 7 and 8 vs entry 6). Remarkably, switching the solvent to DMF led to a superior yield (entry 9). The Sonogashira cross-coupling reaction usually proceeds with Pd/Cu^I catalysts; however, the Cu^I is unnecessary in our catalyst system. Further more, the absence of Cu^I in the reaction medium allowed avoidance of the oxidative Glaser homocoupling of the acetylenic reagent.[4a]

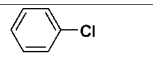
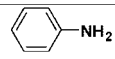
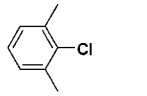
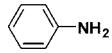
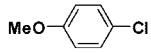
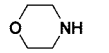
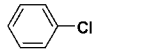
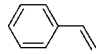
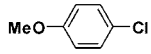
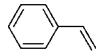
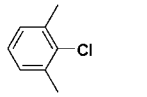
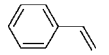
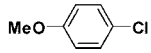
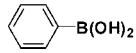
SCHEME 1. Sonogashira Coupling of Aryl Chlorides with Trimethylsilyl Acetylene



Under our optimized reaction conditions (2% $PdCl_2(PPh_3)_2$, 4% P*t*Bu_3, 10% DBU, 1.0 equiv Cs_2CO_3), we accomplished Sonogashira cross-couplings of a wide array of electronically and structurally diverse aryl chlorides in minutes (Table 2). With respect to the aryl chlorides, both electron-neutral and electron-poor aryl chlorides react with alkynes to provide the products

TABLE 3. Microwave-Assisted C−C and C−N Bond-Forming Reactions with Aryl Chlorides



Entry	ArCl	Coupling partner	Yield [%]
1			91
2			90
3			93
4			95
5			91
6			93
7			92

in excellent yields. These conditions were tolerant of aryl chlorides bearing nitrile and ketone substituents (Table 2, entries 5−7, 11, and 20). More remarkable was that even extremely electron-rich aryl chlorides, including 4-chloroanisole and 4-chlorothioanisole, coupled efficiently with alkynes in the presence of this catalyst system (entries 2 and 9). In further experiments to establish the scope of this method, we investigated the cross-coupling of alkynes with heterocyclic chloride. Reactions under these conditions afford high yields of desired products in short reaction times (Table 2, entries 13, 14, 21, and 22). Although sterically hindered substrates are often problematic,[3a,b] the method is also tolerant of *ortho*-substitution in aryl chlorides (Table 2, entries 4 and 7), and even the highly sterically hindered 2-chloro-1,3-dimethylbenzene coupled with phenylacetylene without any difficulty (Table 2, entry 12). Another noteworthy result is the efficient coupling between phenylacetylene and 1-chloro-2-methylpropene (Table 2, entry 15). To the best of our knowledge, the vinyl chlorides were rarely reported as coupling partners in Sonogashira processes.[5] The successful reaction reveals that the present catalyst system is also effective in the cross-coupling reactions of alkynes with vinyl halides. In comparison to phenylacetylene, use of 1-octyne generally gives superior yields of corresponding products (Table 2, entries 16−22).

Interestingly, application of trimethylsilyl acetylene under the same conditions led predominantly to the corresponding diaryl acetylenes (Scheme 1). These results indicated that the present catalyst system also displayed the high catalytic activity to catalyze the cross-coupling reaction of aryl chlorides with 1-aryl-2-(trimethylsilyl) acetylene via activation of the C−Si bond.[4f]

We also proceeded to examine its utility in several different Pd-catalyzed C−C and C−N bond-forming reactions using the MW-assisted method. Remarkably, this protocol can indeed be extended successfully to the Suzuki coupling and Buchwald−Hartwig amination, as well as the Heck coupling with unreactive aryl chlorides. The best conditions for these reactions were similar to those for Sonogashira coupling. In addition, it was observed that whereas $PdCl_2(PPh_3)_2$ was the preferred palladium source for the Sonogashira coupling, $Pd(OAc)_2$ gave the higher conversion for the other types of reactions. As can be seen from the results compiled in Table 3, it is important to note that very high yields can be obtained for these reactions by using representative sterically hindered aryl chloride and electron-rich aryl chloride as starting materials.

In summary, we have described a solution to a longstanding challenge in Sonogashira coupling reaction: the development of a rapid and efficient method for the cross-coupling of unactivated aryl chlorides. Our catalytic system, which employs commercially available components, is also effective for Suzuki coupling, Buchwald-Hartwig amination, and Heck coupling reactions with unactivated aryl chlorides. A broad spectrum of substrates coupled effectively under MW irradiation to provide the desired products in minutes. The short reaction times and simple reaction conditions coupled with a broad substrate scope render this method particularly attractive for the efficient preparation of biologically and medicinally interesting molecules. Given that numerous alkynes, anilines, olefins, and inexpensive aryl chlorides are readily available, the method demonstrated could be readily adopted to prepare large libraries rapidly, and the versatility of this methodology is suitable for library synthesis in drug discovery efforts.

Experimental Section

General Procedure for the Synthesis of 1,2-diphenylethyne (Table 2, entry1). A mixture of chlorobenzene (56 μL), phenylacetylene (50 μL), and Cs_2CO_3 (148 mg) was dissolved in DMF (1.5 mL). Two mole percent $PdCl_2(PPh_3)_2$, 4 mol % P*t*Bu$_3$, and 10 mol % DBU subsequently were added under nitrogen. The vial was sealed, and this mixture was then irradiated for 10 min at 150 °C. After the reaction was cooled to ambient temperature, the crude reaction mixture was diluted with ethyl acetate and then filtered through celite. The filtrate was washed three times with brine, and the combined aqueous phase was extracted with ethyl acetate. The combined organic layers were dried with Na_2SO_4, concentrated, and purified by flash column chromatography (petroleum ether/ethyl acetate) to give the expected product (see Supporting Information for details).

(5) (a) Moonen, N. N. P.; Pomerantz, W. C.; Gist, R.; Boudon, C.; Gisselbrecht, J. -P.; Kawai, T.; Kishioka, A.; Gross, M.; Irie, M.; Diederich, F. *Chem. Eur. J.* **2005**, *11*, 3325. (b) Lemay, A. B.; Vulic, K. S.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 3615.

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Supporting Information Available: Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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